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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SDR/25706	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 03/02665	International filing date *(day/month/year)* 20.06.2003	Priority date *(day/month/year)* 20.06.2002
International Patent Classification (IPC) or both national classification and IPC A61K38/50		
Applicant BIO-CANCER TREATMENT INTERNATIONAL LIMITED		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.01.2004	20.07.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Young, C Telephone No. +49 89 2399-7877

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/02665

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-32 as originally filed

Claims, Numbers

1-30 as originally filed

Drawings, Sheets

1/46-46/46 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

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5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-30
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-30
Industrial applicability (IA)	Yes:	Claims	1-30
	No:	Claims	

2. Citations and explanations

   see separate sheet

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Re Item I

Basis of the opinion

The examination is being carried out on the **following application documents:**

Text for the Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PL PT RO SE SI SK TR

Description, pages:

1-32 as originally filed

Claims, No.:

1-30 as originally filed

Drawings, sheets:

1/46-46/46 as originally filed

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents/:

D1:DATABASE EMBL [Online] Human liver arginase HSARGL, 7 January 1987 (1987-01-07) HARAGUCHI: 'complete CDS of human arginase' retrieved from EBI Database accession no. M14502 XP002258160

D2:SAVOCA K V ET AL: 'CANCER THERAPY WITH CHEMICALLY MODIFIED ENZYMES. II. THE THERAPEUTIC EFFECTIVENESS OF ARGINASE AND ARGINASE MODIFIED BY THE COVALENT ATTACHMENT OF POLYETHYLENE GLYCOL ON THE TAPER LIVER TUMOR AND THE L5178Y MURINE LEUKEMIA' CANCER BIOCHEMISTRY BIOPHYSICS, GORDON AND BREACH SCIENCE PUBLISHER, INC, US, vol. 7, no. 3, 1994, pages 261-268, XP008007608 ISSN: 0305-7232

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Novelty, Article 33 (2) PCT

Claim 1 refers to an isolated recombinant human arginase I having substantially the same amino acid sequence set forth in Figure 2C of the application and having a purity of 80-100%. D1 discloses the nucleic acid and protein sequence of this very protein. However, as a database entry it does not disclose pure protein *per se*, consequently novelty is formally acknowledged. Thus, claims 1-11 are considered to be novel.
The cited prior art is silent with respect to Bacillus based production methods. Thus claims 12-16 are considered novel.
Claims 17-25 recite human arginase I as a pharmaceutical composition. Claims 26 to 30 relate to medical applications of recombinant human arginase *inter alia* its use to treat cancer. D1 as mentioned above discloses the sequence of human arginase alone whilst D2 discloses the use of bovine arginase to treat Taper liver tumor. Consequently novelty is acknowledged for these claims.

Inventive step, Article 33 (3) PCT

Essentially the claimed invention relates to the use of recombinant human arginase I for the treatment of human malignancies, *inter alia* cancer. The application claims recombinant pure human arginase, PEG modified forms, methods of production and pharmaceutical compositions containing human arginase.

The closest prior art is considered to be D2. D2 discloses the use of bovine arginase in an animal model in a pharmaceutical acceptable form i.e. PEG modified. The data show convincing anti-tumor properties for Taper liver tumor. The paper frequently mentions the need for lowered immogenicity and argues strongly in favour of PEGisation. In the case of leukemia the bovine arginase was not shown to be effective in treatment. The paper speculates that this is due to low Km value.

The objective problem is defined as;

" the provision of an alternative arginase based method for treating malignancies"

D1 discloses the entire sequence of human arginase I, thus the cloning or production of this protein can not be considered inventive in light of D1 and standard cloning and expression methods available to the skilled person at the time of filing the present application. Thus, claims 1- 6, 12-16 are not inventive and thus do not meet the requirements of Article 33 (3) PCT.

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Claims 7-11,17-30 relate to PEG modified forms of human recombinant arginase having defined Km values as either pharmaceutical compositions or their uses to treat human malignancies.

In light of D2 the skilled person is faced with the problem arising from low Km of the bovine arginase when treating leukaemia. The skilled person thus has an incentive to improve on the method disclosed in D2. He would in light of the teachings of D2 solve the problem bearing in mind the difficulties with regard to the importance of immunoreactivity. Given that D1 discloses human arginase the skilled person is in a "one way street situation" as it would be expected by the skilled person that this protein would give the best immunological tolerance, he would automatically use this arginase to treat human malignancies just as the authors of D2 used bovine arginase to study/treat malignancies in their animal model. Furthermore PEGation to further reduce immunogenicity is obvious in light of D2.

Improvement in Km demonstrated for human arginase is a bonus effect which as a result of the one way street situation described above can not even justify recognition of inventive step in terms of having unexpected effects.

In short said claims are trivial application of the known sequence of human arginase in light of the teachings of D2. Consequently Claims 1-30 fall short of the requirements of Article 33 (3) PCT.